REMARKS

Claims 1-3, 7-15 and 19-24 are pending. Claims 22-24 have been amended to better define Applicants' invention. New claims 25-27 have been added.

The Office Action states that claims 13 and 14 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 13 recites that the bone comprises cells comprising osteoblasts, periosteal cell, stromal bone marrow cells, satellite cells of muscle tissue, or mesenchymal stem cells, or a combination thereof. It is submitted that osteoblasts, periosteal cell, stromal bone marrow cells, satellite cells of muscle tissue, or mesenchymal stem cells are a subset of cells that bone might comprise. Thus, claim 13 is understood to comply with 37 CFR 1.75(c).

Claim 14 recites that the cartilage comprises cells comprising chondroblasts or mesenchymal stem cells. It is submitted that chondroblasts or mesenchymal stem cells are a subset of cells that cartilage might comprise. Thus, claim 14 is understood to comply with 37 CFR 1.75(c).

The Office Action states that claims 1-3, 7, 13, 14, 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over United States Patent No. 5,998,457 to Kaddurah-Daouk ("Kaddurah") in view of United States Patent No. 4,772,591 to Meisner ("Meisner"), United States Patent No. 5,888,553 to Grant *et al.* ("Grant"), United States Patent No. 5,756,496 to Beale *et al.* ("Beale '496") and United States Patent No. 5,716,926 to Beale *et al.* ("Beale 926").

The Office Action states:

> 6. Kaddurah-Daouk teaches a method of treating osteoporosis or osteoarthritis comprising administering therapeutical effective amount of creatine compound, or a pharmaceutical acceptable salt, to patient. See, particularly, the abstract, table 1-2, and claims 1-12.
>
> 7. Kaddurah-Daouk does not teach expressly the employment of creatine pyruvate for the treatment, or the particular amount administered, or the method may be employed for promoting growth and mineralization of bone;

improving acceptance and osseous integration of bone; or accelerating healing as claimed in claims 22-24.

8. However, Grant et al. teaches that the excess of cortisol is known to be a cause of osteoporosis, tissue degeneration, and an anabolic composition with anticortisol effect are used to balance effect of cortisol. The anabolic composition comprising creatine. See, column 1, line 52 bridging column 2, line 59, column 5, lines 56-65.and claim 8. Meisner teaches a method for accelerated wound healing or treating degenerative disorders including periodontal disease osteoarthritis, comprising administering a composition comprising creatine to an animal or human. See, particularly, column 1, line 28 bridging column 2, line 45, column *5,* lines 3 bridging column 7, line 10. Beale ('496) teaches creatine pyruvate (pyruvyl-creatine) is particularly useful as cortisol antagonist or cortisol blocker for prevent the catabolic activity of cortisol. See column 1, lines 7-18, 54-60; column 3, lines 46-63. Beale (''926) further teaches that pyruvate is known to be useful for treating osteoporosis. See, claim 24.

It is submitted that even if the Examiner's characterization of the references were correct, the cited references provide no motivation to combine the cited references to obtain the presently recited method of treating at least one bone or cartilage condition. "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." In Re Gary E. Geiger,815 F.2d 686, 688 (Fed. Cir. 1987). The Office Action has not pointed to any motivation in the cited references and Applicants have found none. Even assuming that one of skill in the art might find it obvious to try various combinations of agents for treating bone or cartilage conditions, this alone would not support the rejection because obviousness to try is not the standard of 35 U.S.C. § 103. In Re Geiger at 688 (citing In Re Goodwin, 576 F.2d 375, 377 (Fed. Cir. 1978)). In view of the above, Applicants respectfully submit that the Office Action does not set forth a prima facie case of obviousness for the method of claim 1, which recites administering to an animal a therapeutically effective amount of an agent comprising creatine, or an analogue or pharmaceutically acceptable salt thereof, to treat bone or cartilage conditions.

The Office Action states that claims 22-24 are:

> obvious because creatine is known to be useful for promoting tissue repair process, and treating osteoarthritis and osteoporosis would also considered as a process of promoting tissue (cartilage) repairing since one of the major symptoms of osteoarthritis and osteoporosis is tissue degeneration.

Claim 22, as amended herein, recites a method of promoting growth and mineralization of bone or cartilage cells and tissues which comprises administering to a subject in need of such treatment a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof, to promote growth and mineralization of bone or cartilage therein.

It is submitted that the cited references do not disclose or suggest promotion of growth and mineralization of bone or cartilage cells and tissues by administration of creatine pyruvate as presently recited in claim 22. Neither the Office Action nor the cited references provide motivation to modify the references to combine creatine and pyruvate in a method for promoting growth and mineralization of bone or cartilage cells and tissues. An obviousness rejection based upon a combination of references requires a showing of a teaching, suggestion or incentive supporting the combination. In Re Geiger at 688.

Enhancement of protein concentration or muscle mass using a composition comprising pyruvate and an anti-cortisol compound, as disclosed by Beale '469, or the treatment of osteoporosis using calcium pyruvate, as disclosed by Beale '926, would not have given one an expectation of success in promoting growth and mineralization of bone or cartilage cells and tissues by administration of creatine pryuvate, as recited in claim 22. In view of the above, the Office Action does not set forth a prima facie case of obviousness for the method of claim 22.

As presented herein, claim 23 recites a method for improving acceptance and osseous integration of bone implants. The method comprises: administering a therapeutically effective amount of an agent comprising (1) creatine or an analogue thereof or (2) a pharmaceutically acceptable salt of creatine or an analog thereof.

No combination of the cited references discloses, suggests, or teaches administration of creatine to improve acceptance and osseous integration of bone implants. Indeed, the cited references are silent with respect to bone implants. Thus, the cited references fail to disclose, suggest, or teach the totality of the invention set forth in claim 23.

Moreover, even assuming *arguendo* that the cited references contemplate treatment of bones not having implants, such disclosure would not have given one a reasonable expectation of success in improving acceptance and osseous integration of bone implants. Thus, the Office Action fails to set forth a prima facie case of obviousness with respect to claim 23, as amended.

Claim 24, as presented herein, recites a method for accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma or surgery, which method comprises administering to the subject a therapeutically effective amount of (1) a creatine compound or analogue thereof or (2) a pharmaceutically acceptable salt of creatine or analog thereof, or (3) a creatine kinase.

No combination of the cited references discloses or suggests administration of creatine for accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma or surgery. Indeed, the cited references are silent with respect to defects in bone or cartilage caused by trauma or surgery. Moreover, even assuming *arguendo* that the cited references contemplate treatment of bone not subjected to trauma or surgery, such disclosure would not have given one a reasonable expectation of success in achieving success in accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma or surgery, as set forth in claim 24. Thus, the Office Action fails to set forth a prima facie case of obviousness with respect to claim 24, as amended.

New claim 25, recites a method of treating at least one of (1) osteoporosis unrelated to weight gain or weight loss and (2) osteoarthritis unrelated to weight gain or weight loss, which comprises administering to an animal a therapeutically effective amount of an agent comprising creatine or an analogue or pharmaceutically acceptable salt thereof.

It is submitted that no combination of the cited references discloses, suggests, or teaches treatment of at least one of (1) osteoporosis unrelated to weight gain or weight loss and (2) osteoarthritis unrelated to weight gain or weight loss, as presently recited in claim 25. Unlike the invention of claim 25, Kaddurah specifically seeks to treat disorders related to weight gain or weight loss and is silent with respect to treatment of disorders unrelated to weight gain or weight loss. Because disorders unrelated to weight gain or weight loss may differ from disorders related to weight gain or weight loss, Kaddurah, taken alone or in

combination with other cited references, would not have given one an expectation of success in achieving the invention of claim 25.

New claim 27 recites a method of treating at least one bone or cartilage condition which comprises administering to an animal a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof, to treat at least one of osteoporosis, osteoarthritis, and periodontitis. It is submitted that no combination of the cited references discloses, suggests, or teaches the invention of claim 27.

In view of the foregoing amendments and remarks, it is believed that the rejections in the Office Action have been overcome. Insofar as the foregoing comments with respect to the independent claims are equally applicable to their respective dependent claims, the rejections of the dependent claims are also believed to have been overcome for this reason as well as others presented herein. Applicants respectfully submit that the prior art cited in this case taken individually or in combination neither discloses nor suggests the inventions recited in independent claims 1, 22-25 and 27. Thus, the claims as presented and amended herein are submitted to be in condition for allowance.

Other than the fees for the Extension of Time and additional claims authorized on the accompanying fee sheets, no fee is believed due for this submission. Should other fees be required, however, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

If the Examiner wishes to discuss this case, then Applicants respectfully request a personal or telephonic interview to discuss any remaining issues and expedite the allowance of the application.

Respectfully submitted,

Date December 18, 2002

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Enclosure

APPENDIX A

Marked up copy of amended claims.

22. A method of promoting growth and mineralization of bone or cartilage cells and tissues which comprises administering to a subject in need of such treatment a therapeutically effective amount of an agent comprising creatine pyruvate[,] or an analogue [or pharmaceutically acceptable salt] thereof, to promote growth and mineralization of bone or cartilage therein.

23. (Amended) A method of improving acceptance and osseous integration of bone implants which comprises administering to a subject in need of such treatment a therapeutically effective amount of an agent comprising (1) creatine or an analogue thereof or (2) a pharmaceutically acceptable salt of creatine or analog thereof, to improve acceptance and osseous integration of bone implants.

24. (Amended) A method for accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma[,] or surgery, [or a degenerative disease,] which method comprises administering to the subject a therapeutically effective amount of (1) a creatine compound[,] or analogue thereof or (2) a pharmaceutically acceptable salt of creatine or analog thereof, or (3) a creatine kinase.

Please add the following new claims:

25. A method of treating at least one of (1) osteoporosis unrelated to weight gain or weight loss and (2) osteoarthritis unrelated to weight gain or weight loss, which comprises administering to an animal a therapeutically effective amount of an agent comprising creatine or an analogue or pharmaceutically acceptable salt thereof, to treat the at least one of (1) osteoporosis unrelated to weight gain or weight loss and (2) osteoarthritis unrelated to weight gain or weight loss.

26. The method of claim 25, wherein the agent comprises creatine pyruvate.

27. A method of treating at least one bone or cartilage condition which comprises administering to an animal a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof, to treat at least one of osteoporosis, osteoarthritis, and periodontitis.